REMARKS

Applicants added new Claims 113-118. Support for the new claims may be found in claims already presented and within the specification. In particular, support for a 20 mg sildenafil citrate tablet is found in Example I at page 10. Furthermore, daily dosage levels are described at page 7, lines 32-35.

35 U.S.C. § 103(a) Rejection of Claims 44-112 Over Ellis et al. (WO 94/28902)

The Examiner maintained the rejection of Claims 44-112 as obvious over Ellis et al. (WO 94/28902). The Examiner contends that Ellis et al. teach compounds that are potent inhibitors of cGMP PDEs, leading to elevated cGmp levels that provide the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension. According to the Examiner, the skilled artisan would be motivated to treat patients with pulmonary hypertension, irrespective of its cause, because Ellis et al discloses that such inhibitors are used to treat both hypertension and pulmonary hypertension. In particular, the Examiner contends that Ellis et al. disclose preferred compounds of formula I, wherein R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the N atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl. Furthermore, the Examiner points out that Ellis et al disclose pharmaceutically acceptable salts of the compounds of formula I, as well as various modes of administration and dosing ranges from 5-75 mg (3 X day). The Examiner contends that determination of optimum dosage is well within the level of one having ordinary skill in the art. According to the Examiner, therefore, Ellis et al render the invention obvious.

Applicants traverse the rejection of Claims 44-112 and request that the Examiner reconsider the rejection in light of the comments herein. In particular, Applicants submit that: (1) the Examiner is incorrectly interpreting Ellis et al to include a disclosure for which there is no basis; (2) In light of (1), Ellis et al. (or the combination of Ellis et al, Bell I and Bell II) do not render obvious Applicants' invention.

(1) Ellis et al. Does Not Teach That All cGMP PDEs Inhibitor Compounds Treat Hypertension and Pulmonary Hypertension.

The Examiner contends that Ellis et al. teach compounds that are potent inhibitors of cGMP PDEs, leading to elevated cGmp levels that provide the basis for many utilities,

namely the treatment of hypertension and pulmonary hypertension. According to the Examiner, the skilled artisan would be motivated to treat patients with pulmonary hypertension, because Ellis et al discloses that such inhibitors are used to treat both hypertension and pulmonary hypertension.

At issue, is the interpretation of what exactly Ellis et al. teach. Applicants respectfully submit that the Examiner is improperly and incorrectly interpreting Ellis et al. to teach a utility (pulmonary hypertension) for which there is no basis for all the compounds disclosed therein. The only new utility taught by Ellis et al. is that the compounds of formula I described in EP0463756 ("Bell I") and EP0526004 ("Bell II"), as well as other disclosed compounds, are useful for the treatment of erectile dysfunction. There is no new teaching that these compounds (the compounds disclosed in Bell I) are useful for treating pulmonary hypertension. The only compounds disclosed as treating pulmonary hypertension are those compounds disclosed in Bell II.

Applicants submit that it is necessary to parse out exactly what the disclosure of Bell I and II is to properly interpret the utility of the compounds described by Ellis in paragraph 2 of page 2. In particular, Bell I disclose a genus of PDE inhibitor compounds of formula I having the general core of the compounds of formula I disclosed in the instant application, wherein, *inter alia,* R^1 is C_1-C_3 alkyl; R^2 is C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl; R^4 taken together with the SO_2N group to which it is attached forms a piperazine, having a substituent R^6 is C_1-C_6 alkyl. The PDE compounds therein are disclosed as having utility in the treatment of various *cardiovascular* disorders, such as angina, *hypertension*, heart failure and atherosclerosis. (*See* page 2, lines 1-5, 11-13).

Sildenafil is a species of the genus of compounds of Bell I described above. Bell I does not, however, disclose the species, sildenafil. Bell I does not disclose *pulmonary* hypertension. There is no basis or suggestion in Bell I for which one of ordinary skill in the art would conclude that the compounds of formula I described therein are (or may be) useful for pulmonary hypertension. The disclosure of Ellis et al., with respect to the disclosure of Bell I, is limited, therefore, to compounds described therein as being useful for the treatment of, *inter alia*, hypertension.

Consequently, there is no basis for the Examiner's interpretation of Ellis et al, that the compounds of formula I described in Bell I now have the additional utility of treating pulmonary hypertension. The Examiner is improperly reading in to Ellis' et al. a utility for compounds of formula I described in Bell I for which there was no previous disclosure.

Bell II disclose a genus of PDE inhibitor compounds of formula I having the general

core of the compounds of formula I disclosed in the instant application, wherein, *inter alia*, R^1 is C_1-C_3 alkyl; R^2 is C_1-C_6 alkyl; R^3 is C_1-C_6 alkyl; R^4 *does not*, however, disclose the 4-methyl-piperazine-1-sulfonyl substituent disclosed in Bell I. The PDE compounds disclosed in Bell II are described as having utility in the treatment of, *inter alia*, pulmonary hypertension.

The genus of compounds described in Bell II *does not* fall within the scope of the genus of the compounds described in Bell I. Accordingly, the compounds of formula I of Bell I differ from the compounds of formula I of Bell II and sildenafil *is not* a species of the genus described in Bell II.

Going back to the disclosure of Ellis et al, where the utilities of the compounds of Bell I and Bell II are described, Ellis et al do not provide any basis or support for expanding the scope of *cardiovascular* utilities for the compounds described in Bell I to include the described utility of *pulmonary* hypertension disclosed in Bell II. In paragraph 2 of page 2, Ellis et al are merely describing the disclosures of Bell I and Bell II. Ellis et al is *not* adding to that disclosure.

Certainly, in paragraph 2 of page 2, one of ordinary skill in the art would not regard that Ellis' invention was that the compounds of Bell I and the compounds of Bell II *all* have the same utility. Nor, would one skilled in the art, reviewing the disclosures of Bell I and Bell II, regard that Ellis was teaching that the compounds of Bell I are useful in treating *pulmonary* hypertension. Instead, the teaching of Ellis et al. is limited to the new utility that the compounds of formula I have the unexpected utility of treating erectile dysfunction. Ellis et al. provide support for the compounds of Bell I and Bell II for this additional new utility. There is no support within Ellis et al. for expanding the utility of the compounds of Bell I to include the additional utility of treating pulmonary hypertension.

In particular, Applicants take issue with the Examiner's interpretation of the following statement in Ellis et al. – that "the utilities *already* disclosed for the compounds in [Bell I and Bell II], namely in the treatment of . . . pulmonary hypertension. . . ." (emphasis added). The Examiner contends that this statement means that the compounds of formula I described in Bell I and in Bell II *all* have the same utilities. Applicants respectfully disagree. Applicants submit that the Examiner has distorted the *plain meaning* of the statement in Ellis et al., wherein Ellis et al merely describe – as background art – utilities ***already*** disclosed in Bell I and Bell II.

According to the Webster's Dictionary, the term "already" is defined as "by or before a certain, past, present, or future; previously; beforehand; by the time specified." Webster's

20th Century Dictionary (2nd Ed.). Consequently, when interpreting the statement of Ellis et al. that "the utilities *already* disclosed for the compounds in [Bell I and Bell II]", the only *reasonable* interpretation is the plain meaning interpretation – the utilities for the compounds of formula I were disclosed in their respective references. It is *not reasonable* to interpret the statement as providing *new utilities* for the compounds of formula I described in Bell I, because according to Ellis et al., the utilities must have *already* been disclosed.

Applicant submits that Ellis et al. are merely describing the disclosure of Bell I and Bell II – there is no further additive teaching by Ellis et al., in the 2nd paragraph of page 2, to expand the utility of those compounds described in Bell I to include the utility of pulmonary hypertension described in Bell II. It is only at the 3rd paragraph that Ellis describes the additional utility of the compounds described in Bell I and Bell II as being useful for the treatment of erectile dysfunction.

For one skilled in the art to fully understand the Ellis et al description of Bell I and Bell II, one skilled in the art would refer back to the respective references to fully understand the disclosures therein. For example, without referring back to Bell I or Bell II, one skilled in the art would not know the chemical structures of the compounds of formula I disclosed in the respective references that are referred to in Ellis et al. Analogously, one skilled in the art would not know the specific utilities disclosed in Bell I and Bell II for the compounds of formula I, without referring back to the respective references to see what those references teach.

Consequently, it is only *reasonable*, and one skilled in the art would conclude, that the compounds disclosed in Bell I have the utility of treating cardiovascular disease, including hypertension. One skilled in the art would not conclude, however, that the compounds of Bell I would also include the utility disclosed in Bell II. It is only by an improper interpretation of the statement in Ellis et al, that one would conclude that new utilities for the compounds of Bell I were disclosed.

Consequently, Applicants request that the Examiner consider the above interpretation, when reviewing Applicants' response below to the obviousness rejection.

(2) Ellis et al. Alone or in Combination with Bell I and Bell II does not Render Applicants' Invention Obvious.

Applicants submit that the Examiner has failed to meet the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103(a). In particular, "when

applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) Reasonable expectation of success is the standard with which obviousness is determined." MPEP § 2141.

(A) The Claimed Invention Must be Considered as a Whole:

Applicants' invention is directed to, *inter alia,* a method of treating pulmonary hypertension comprising administering sildenafil such that pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance in the patient.

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination:

The teachings of the prior art detail various utilities for specific PDE compounds, including hypertension, pulmonary hypertension and erectile dysfunction. As discussed more fully above, Ellis et al., does not disclose that the compounds of formula of Bell I are useful in treating pulmonary hypertension. Ellis does not disclose that sildenafil is useful for treating pulmonary hypertension. Bell I discloses a specific genus of PDE compounds – of which sildenafil is a species, but not disclosed – that are useful in treating cardiovascular disorders, including hypertension. Bell II discloses a different genus of PDE compounds – of which sildenafil *is not* a species – useful for treating, *inter alia*, pulmonary hypertension. None of the references: Ellis et al, Bell I or Bell II disclose that sildenafil is a PDE_5 compound. Furthermore, none of the references disclose that for effective treatment of pulmonary hypertension that pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance in the patient.

Applicants submit that the combination of references – or Ellis et al. alone – do not teach every element of Applicants' invention: administration of sildenafil for the treatment of pulmonary hypertension wherein pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance in the patient.

Viewing the disclosures of Bell I and Bell II, one of ordinary skill in the art would not have a reasonable expectation of success that the compounds of Bell I would have the same pulmonary hypertension utility as those described for the compounds in Bell II.

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention

It is only by improper *hindsight reconstruction* that one of ordinary skill in the art would piece together the disclosures of *three* references: Bell I, Bell II and Ellis et al, to arrive at anything close to applicants' invention – a method of treating *pulmonary* hypertension by administrating sildenafil. Even so, such *hindsight reconstruction* leaves out the limitation that administration must be such that pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance.

Accordingly, Applicants submit that Ellis or the combination of Ellis et al, Bell I and Bell II *does not* render Applicants' invention obvious. At best, as pointed out in earlier responses, Ellis et al (or the combination of the three references: Ellis et al, Bell I and Bell II) would at most made Applicants' invention "obvious to try." Obvious to try, however, is not the proper standard for patentability.

(D) Reasonable Expectation of Success is the Standard

Applicants further submit that one skilled in the art would not have a reasonable expectation of success to arrive at Applicants' invention – administration of sildenafil for the treatment of pulmonary hypertension wherein pulmonary vascular resistance is selectively reduced to a greater extent than systemic vascular resistance in the patient. As discussed above, the treatment of pulmonary hypertension is not disclosed for the genus of compounds disclosed in Bell I, of which sildenafil is a species. Furthermore, the references do not disclose the selective reduction of pulmonary vascular resistance compared to systemic vascular resistance. The only disclosure for pulmonary hypertension lies in Bell II wherein a different genus of compounds is taught.

As Applicants already discussed in previous responses, and as disclosed within Applicants' specification, for a compound to be useful in the long term treatment of chronic pulmonary hypertension, it preferably is *selective* for the *pulmonary* vascular system – not the *systemic* vascular system. If the compound is not selective and impacts the systemic vascular system, the patient would likely suffer adversely from *cardiovascular* hypotension. Applicants' invention is directed to a compound that *preferentially* acts on the *pulmonary* system, instead of the systemic system. Thus, the concern of cardiovascular hypertension is minimized.

Given that the genus of compounds of which sildenafil is a species, is disclosed in Bell I as useful for the treatment of cardiovascular disorders, including hypertension, one of

ordinary skill in the art would not expect that sildenafil -- a species -- would be useful for treating *pulmonary* hypertension. Furthermore, in light of the disclosure of Bell I, one of ordinary skill in the art would not expect that sildenafil would be *selective* for the pulmonary system compared to the systemic system.

When viewing Applicants' invention as a whole, and considering the references as a whole, Applicants submit that Ellis et al (or in combination with Bell I and Bell II) does not suggest the desirability of utilizing sildenafil for the treatment of pulmonary hypertension. Furthermore, Applicants submit that one skilled in the art would not reasonably expect that (1) sildenafil would be useful for the treatment of pulmonary hypertension, given that the genus of compounds is disclosed as being useful for, *inter alia,* cardiovascular hypertension; and (2) sildenafil would act selectively on the pulmonary system compared to the systemic system.

Accordingly, given the above, Applicants maintain that a *prima facie* case of obviousness has not been proven by the Examiner and respectfully request that the Examiner reconsider the rejection in light of the comment made herein.

35 U.S.C. § 103(a) Rejection of Claims 44-112 Over Schudt (U.S. 6,333,354)

The Examiner rejected Claims 44-112 as being obvious in light of Schudt (U.S. 6,333,354). In particular, the Examiner contends that Schudt teaches a method of treating pulmonary hypertension with the administration of a composition that comprises at least a PDE inhibitor and, specifically, sildenafil. According to the Examiner, therefore, the skilled artisan would be motivated to treat patients with pulmonary hypertension, irrespective of the cause, because Ellis et al clearly discloses to the artisan that these inhibitors of PDE are used to treat the same ailment that is claimed in the instant application. Furthermore, the Examiner contends that Schudt teaches the administration of sildenafil without the administration of *inter alia* prostacyclines, oxygen and iloprost. The Examiner further notes that it is well within the level of a skilled artisan to determine dosage and optimum therapeutic administration (*e.g.* inhalation) to maximize the effect of the drug, while minimizing adverse side-effects.

Applicants traverse the obviousness rejection of Claims 44-112 in light of Schudt and submit that the Examiner has not made a *prima facie* case of obviousness.

Schudt discloses a superadditive increase in the action of an AC or GC agonist on the level and duration of the pulmonary blood pressure due to the simultaneous administration of a PDE inhibitor in isolated perfused rabbit lung. Col. 3 (lines 16-19).

Because of the superadditive effect seen in isolated rabbit lung, Schudt discloses an extensive list of possible indications that may be treated, including pulmonary hypertension. (Col. 3, lines 38-54). Specifically, Schudt discloses as one embodiment the combined use of a PDE inhibitor, including sildnafil, and a guanylate cyclase agonist for the above-mentioned disease states. Id. at lines 55-60. Applicants are unable to locate the disclosure wherein the Examiner states Schudt teaches the administration of sildenafil without the administration of *inter alia* prostacyclines, oxygen and iloprost. Furthermore, Schudt does not specifically disclose sildenafil – in combination or alone – as specifically being useful for the treatment of pulmonary hypertension.

Schudt does not disclose results in humans. Schudt does not disclose oral administration of sildenafil or other PDE inhibitors. Instead, Schudt discloses inhalation or infusion. Schudt does not suggest that sildenafil may be administered at dosages such that the pulmonary system is *preferentially* acted upon, instead of the systemic system. Schudt does not suggest that sildenafil may be administered alone for the treatment of pulmonary hypertension.

In fact, one of ordinary skill in the art, reading the disclosure of Schudt, would believe that administration of sildenafil without a guanylate cyclase agonist would not successfully treat the disease disclosed, including pulmonary hypertension, especially in light of the following statement:

> As a result of the combination according to the invention of PDE inhibitor and AC agonist or GC agonist, the individual components can be used in concentrations which are not very active or *not active at al on their own*.

Col. 3, lines 26-29. Schudt indicates that the individual compounds may not be active themselves. This is not the case with sildenafil. As disclosed within Applicants' specification, sildenafil is surprisingly effective in treating pulmonary hypertension. It is so effective that the FDA approved the sale of sildenafil for the treatment of pulmonary hypertension under the tradename of Revatio™. One of ordinary skill in the art, reading the disclosure of Schudt, would certainly not expect that sildenafil alone – not in combination with the agonists described therein – would be so effective, since Schudt teaches that a "superadditive" effect is seen by the combination in rabbit lung. Consequently, Schudt teaches away from Applicants' invention, instead of suggests Applicants' invention.

Given the above, Applicants submit that one of ordinary skill in the art would not be motivated by Schudt to arrive at Applicants' invention – the *oral* administration of sildenafil for the treatment of pulmonary hypertension by the preferential activity on the pulmonary

system compared to the systemic system. A *prima facie* case of obviousness has not been made. Accordingly, Applicants respectfully request that the Examiner reconsider the rejection of Claims 44-112, in light of the above comments.

CONCLUSION

Applicants respectfully request consideration of the remarks above. Applicants encourage the Examiner to contact the undersigned, if further issues remain, so that allowance of this application may be expedited

Respectfully submitted,

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